GenCore version 5.1.3

OM protein - protein search, using sw model

Run on: December 30, 2002, 16:14:27 ; Search time 35 Seconds
(without alignments)
247.465 Million cell updates/sec

Title: US-09-664-326-23
Perfect score: 368
Sequence: 1 LTYTDCTESGQNLCLCEGSN.....PKPQSHNDGDFEEIPEEYLQ 65

Scoring table: BLOSUM62
Gapop 10.0 , Gapext 0.5

Searched: 908470 seqs, 133250620 residues

Total number of hits satisfying chosen parameters: 908470

Minimum DB seq length: 0
Maximum DB seq length: 2000000000

Post-processing: Minimum Match 0%
Maximum Match 100%
Listing first 45 summaries

Database : A_Geneseq_101002:*
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Pred. No. is the number of results predicted by chance to have a score greater than or equal to the score of the result being printed, and is derived by analysis of the total score distribution.

SUMMARIES

Result No.	Score	% Query Match	Length	DB	ID	Description
1	368	100.0	65	10	AAP90359	Hirudin derivative
2	368	100.0	65	16	AAR78291	Desulphatohirudin
3	368	100.0	65	16	AAR79813	Hirudin derivative
4	368	100.0	65	17	AAW13897	Hirudin variant (L
5	368	100.0	65	17	AAW03735	Recombinant hirudi
6	368	100.0	65	18	AAW11527	Recombinant hirudi
7	368	100.0	65	22	AAB70828	S. marcescens hiru
8	368	100.0	127	23	ABB08618	Hir(1-65)/AspPro/T
9	365	99.2	65	17	AAW13896	Hirudin variant (d
10	364	98.9	64	6	AAP50082	Anticoagulant pept
11	363	98.6	64	15	AAR59773	Desulphatohirudin.
12	360	97.8	65	6	AAP50329	Hirudin protein.
13	360	97.8	65	6	AAP50335	Hirudin variant.
14	360	97.8	65	6	AAP50188	Desulphatohirudine
15	360	97.8	65	8	AAP70225	Sequence of desulp
16	360	97.8	65	12	AAR12887	Synthetic hirudin
17	360	97.8	65	13	AAR24308	Hirudin HV-1. Syn
18	360	97.8	65	14	AAR30486	Hirudin HV1. Hiru
19	360	97.8	65	15	AAR54636	Anticoagulant hiru
20	360	97.8	65	15	AAR59767	Desulphatohirudin
21	360	97.8	65	16	AAR62214	HV1 derivative of
22	360	97.8	65	16	AAR69099	Hirudin variant 1
23	360	97.8	65	17	AAR99354	Hirudin variant HV
24	360	97.8	65	17	AAW13889	Hirudin variant (I
25	360	97.8	65	18	AAW21762	Hirudin, fused to
26	360	97.8	65	19	AAY82265	Hirudin variant rH
27	360	97.8	65	23	ABB77700	Hirudin amino acid
28	360	97.8	66	7	AAP60395	Desulphatohirudin.
29	360	97.8	66	12	AAR10969	HV-1. Synthetic.
30	360	97.8	66	13	AAR31209	Desulphatohirudin
31	360	97.8	66	13	AAR31210	Desulphatohirudin
32	360	97.8	66	17	AAW13892	Hirudin variant (P
33	360	97.8	69	13	AAR24309	Hirudin (HV-1) RGD
34	360	97.8	69	13	AAR24312	Hirudin (HV-1) RGD
35	360	97.8	70	13	AAR24315	Hirudin (HV-1) GRE
36	360	97.8	71	13	AAR24327	Hirudin (HV-1) GKD
37	360	97.8	72	13	AAR24321	Hirudin (HV-1) CRG
38	360	97.8	72	13	AAR24324	Hirudin (HV-1) CKG
39	360	97.8	77	13	AAR24318	Hirudin (HV-1) HHL
40	360	97.8	82	15	AAR54088	PHO5 leader and hi
41	360	97.8	82	15	AAR51073	Yeast PHO5 signal
42	360	97.8	92	12	AAR14151	MSP signal peptide
43	360	97.8	93	15	AAR47489	HV-1 encoded by su
44	360	97.8	93	15	AAR47490	Desulphatohirudin
45	360	97.8	134	12	AAR12888	Factor Xa-cleavabl

ALIGNMENTS

RESULT 1
AAP90359
ID AAP90359 standard; protein; 65 AA.
XX
AC AAP90359;
XX
DT 01-NOV-1989 (first entry)
XX
DE Hirudin derivative.
XX
KW Hirudin deriv; thrombin inhibitor.
XX
PN EP324712-A.
XX
PD 19-JUL-1989.
XX
PF 13-JAN-1988; 88EP-0805540.
XX
PR 13-JAN-1988; 88DE-3805540.
XX
PA (FARH) HOECHST AG.
XX
PI Crause P, Habermann P, Tripier D;
XX
DR WPI; 1989-208655/29.
XX
PT New hirudin deriv. with N-terminal leucine - is expressed in high
PT yields in yeasts and is secreted in form with correct folding.
XX
PS Claim 1; page 8; 11pp; German.
XX
CC The hirudin deriv. has thrombin-inhibiting activity. Unlike
CC analogues with N-terminal Thr-Tyr or Ile-Tyr units, it is

```
CC   expressed in high yields  in yeasts and is secreted in a
CC   form with correct folding.
XX
SQ   Sequence   65 AA;

  Query Match            100.0%;  Score 368;  DB 10;  Length 65;
  Best Local Similarity   100.0%;  Pred. No. 1.8e-28;
  Matches   65;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy      1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60
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Db      1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60

Qy     61 EEYLQ 65
          |||||
Db     61 EEYLQ 65


RESULT 2
AAR78291
ID   AAR78291 standard; protein; 65 AA.
XX
AC   AAR78291;
XX
DT   06-MAR-1996  (first entry)
XX
DE   Desulphatohirudin HV1.
XX
KW   Desulphatohirudin; leech; Hirudo medicinalis; anticoagulant; sugar;
KW   stability; therapy.
XX
OS   Hirudo medicinalis.
XX
PN   WO9520399-A1.
XX
PD   03-AUG-1995.
XX
PF   25-JAN-1995;   95WO-IB00053.
XX
PR   26-JAN-1994;   94GB-0001447.
XX
PA   (CIBA ) CIBA GEIGY AG.
XX
PI   Arvinte T;
XX
DR   WPI; 1995-275296/36.
XX
PT   New freeze dried hirudin compositions - contg. potassium phosphate
PT   and a sugar to provide long term storage stability at ambient temps.
XX
PS   Disclosure; Page 3; 22pp; English.
XX
CC   The amino acid sequence of the desulphatohirudin composition HV1.
CC   The hirudin cpds. AAR78290-4 can be isolated from leeches (Hirudo
CC   medicinalis).  The cpds. have anticoagulant properties and are
CC   useful in compositions contg. the hirudin, potassium phosphate and
CC   a sugar pref. mannitol, trehalose, sucrose, etc.  The potassium
CC   phosphate has been found to increase the stability of the hirudin
CC   cpd. esp. at ambient temp.  The compsns. contg. the hirudin can be
CC   used for anticoagulant therapy.
XX
SQ   Sequence   65 AA;

  Query Match            100.0%;  Score 368;  DB 16;  Length 65;
  Best Local Similarity   100.0%;  Pred. No. 1.8e-28;
  Matches   65;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy      1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60
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Db      1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60

Qy     61 EEYLQ 65
          |||||
Db     61 EEYLQ 65


RESULT 3
AAR79813
ID   AAR79813 standard; protein; 65 AA.
XX
AC   AAR79813;
XX
DT   28-MAR-1996  (first entry)
XX
DE   Hirudin derivative.
XX
KW   Hirudin; derivative; anticoagulant; polyethylene glycol.
XX
OS   Synthetic.
XX
PN   EP667355-A1.
XX
PD   16-AUG-1995.
XX
PF   06-FEB-1995;   95EP-0101554.
XX
PR   10-FEB-1994;   94DE-4404168.
XX
PA   (FARH ) HOECHST AG.
XX
PI   Hropot M,  Ludwig J,  Obermeier R,  Tripier D;
XX
DR   WPI; 1995-276615/37.
XX
PT   New hirudin deriv. with amine deriv. attached to position 36 or 63
PT   - useful as anticoagulants, partic. for transdermal delivery by
PT   iontophoresis.
XX
PS   Disclosure; Page 8; 14pp; German.
XX
CC   Hirudin derivatives of formula A0-A1-A2-(Hirudin 3-36)-(Y)=(Hirudin
CC   37-65) have anticoagulant activity, especially those derivatised
CC   with polyethylene glycol. In the formula A0, A1 and A2 are amino
CC   acid residues and A0 can also be H, Y is a residue of amines NH2-R-X
CC   or A-R1-X, where A is 1-10 amino acids, R is a 1-10C alkyl (opt.
CC   substituted), R1 is either H, a covalent bond, 1-10 sugar residues
CC   or -(O-(CH2)m)n where m is 2-5 and n is 1-100.  X is H, OR2, NHR2, C
CC   OOR2 or an amino acid. R2 is H or as R.  The = sign denotes that the
CC   two hirudin fragments are connected by disulphide bridges.
XX
SQ   Sequence   65 AA;

  Query Match            100.0%;  Score 368;  DB 16;  Length 65;
  Best Local Similarity   100.0%;  Pred. No. 1.8e-28;
  Matches   65;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy      1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60
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Db      1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60

Qy     61 EEYLQ 65
          |||||
Db     61 EEYLQ 65


RESULT 4
AAW13897
ID   AAW13897 standard; Protein; 65 AA.
XX
AC   AAW13897;
XX
DT   14-MAY-1997  (first entry)
XX
DE   Hirudin variant (Leu 1, Thr 2)-desulphato hirudin HV1.
XX
KW   Hirudin; variant; thrombin inhibitor; human; acetylsalicylic acid; ASA;
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```
KW   thrombolytic agent; cardiovascular event; stroke; cardiovascular death;
KW   coronary re-vascularisation; therapy; acute myocardial infarction; AMI;
KW   hirudo medicinalis.
XX
OS   Synthetic.
XX
FH   Key             Location/Qualifiers
FT   Misc-difference 1
FT                   /label= V1L
FT   Misc-difference 2
FT                   /label= V2T
FT   Modified-site   63
FT                   /note= "modified with phenolic hydroxy group"
XX
PN   EP732102-A2.
XX
PD   18-SEP-1996.
XX
PF   12-MAR-1996;   96EP-0103821.
XX
PR   12-MAY-1995;   95US-0440556.
PR   15-MAR-1995;   95US-0405269.
XX
PA   (BEHW ) BEHRINGWERKE AG.
PA   (BGHM ) BRIGHAM & WOMENS HOSPITAL.
XX
PI   Heinrichs H,  Hennekens CH;
XX
DR   WPI; 1996-414245/42.
XX
PT   Composition comprising acetyl:salicylic acid and hirudin - is esp.
PT   useful for preventing the recurrence of acute myocardial
PT   infarction(s)
XX
PS   Claim 6; ; 11pp; English.
XX
CC   AAW13889-W13898 represent mutations of the hirudin variants represented
CC   by AAR99354-R99356.  Hirudin is a direct thrombin inhibitor, which has a
CC   very high affinity for human (as well as other mammalian species)
CC   thrombin. One molecule binds to a thrombin molecule, forming a tight
CC   noncovalent complex and thereby irreversibly inactivates thrombin.  These
CC   sequences can be used in a composition of the invention, which also
CC   contains acetylsalicylic acid (ASA).  The composition may be administered
CC   to patients not undergoing treatment with a thrombolytic agent, to
CC   inhibit and/or prevent myocardial or cardiovascular events (including
CC   myocardial infarctions, strokes, coronary re-vascularisation or
CC   cardiovascular death) in the patient. The compositions of the invention
CC   are especially useful for preventing the recurrence of acute myocardial
CC   infarctions (AMI).  The components ASA and hirudin act synergistically.
CC   The combined use of ASA and hirudin in AMI patients where thrombolytic
CC   treatment is not advisable is expected to result in a higher incidence of
CC   open coronary vessels.
XX
SQ   Sequence   65 AA;

  Query Match             100.0%;  Score 368;  DB 17;  Length 65;
  Best Local Similarity   100.0%;  Pred. No. 1.8e-28;
  Matches   65;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

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Db      1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60

Qy     61 EEYLQ 65
          |||||
Db     61 EEYLQ 65


RESULT 5
AAW03735
ID   AAW03735 standard; protein; 65 AA.
XX
AC   AAW03735;
XX
DT   17-OCT-1996  (first entry)
XX
DE   Recombinant hirudin analogue for admin. by intravenous drip injection.
XX
KW   Hirudin; anti-coagulant; disseminated intravascular coagulation; DIC;
KW   thrombin inhibitor; low dosage; reduced side-effects; bleeding.
XX
OS   Synthetic.
XX
PN   JP08143470-A.
XX
PD   04-JUN-1996.
XX
PF   18-NOV-1994;   94JP-0284910.
XX
PR   18-NOV-1994;   94JP-0284910.
XX
PA   (FARH ) HOECHST JAPAN KK.
XX
DR   WPI; 1996-318859/32.
XX
PT   Admin. of specific, lower dosage of hirudin or analogue by
PT   intravenous drip injection - reduces side-effects in treatment of
PT   disseminated intravascular coagulation
XX
PS   Claim 3; Page 2; 5pp; Japanese.
XX
CC   The present sequence is that of the preferred hirudin analogue to be
CC   administered in a novel intravenous drip injection for treatment of
CC   disseminated intravascular coagulation. The hirudin molecule is
CC   formulated at a concentration of 0.005-0.038 mg/ml (50-380 ATU/ml);
CC   admin. of a reduced dosage of hirudin suppresses unwanted bleeding.
XX
SQ   Sequence   65 AA;

  Query Match             100.0%;  Score 368;  DB 17;  Length 65;
  Best Local Similarity   100.0%;  Pred. No. 1.8e-28;
  Matches   65;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy      1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60
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Db      1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60

Qy     61 EEYLQ 65
          |||||
Db     61 EEYLQ 65


RESULT 6
AAW11527
ID   AAW11527 standard; protein; 65 AA.
XX
AC   AAW11527;
XX
DT   11-SEP-1997  (first entry)
XX
DE   Recombinant hirudin derivative.
XX
KW   hirudin; recombinant; derivative; treatment; prevention; brain tissue;
KW   cellular infiltration; polynuclear leukocyte; monocyte; macrophage;
KW   inhibit; vimentin positive astrocyte; anti-inflammatory.
XX
OS   Synthetic.
XX
PN   JP08310967-A.
XX
PD   26-NOV-1996.
XX
PF   17-MAY-1995;   95JP-0118388.
XX
PR   17-MAY-1995;   95JP-0118388.
XX
```

PA (FARH) HOECHST JAPAN LTD.
XX
DR WPI; 1997-061735/06.
XX
PT Agent for treatment and prevention of brain tissue damage -
PT comprises hirudin or deriv. as active ingredient to inhibit damage
PT caused by inflammatory cell infiltration
XX
PS Claim 3; Page 2; 5pp; Japanese.
XX
CC This sequence is a preferred recombinant hirudin derivative for use as
CC an agent for treatment and prevention of brain tissue damage,
CC particularly secondary damage caused by cellular infiltration of
CC polynuclear leukocytes or the monocyte/macrophage system. The agent is
CC effective against damage caused by inflammatory cells and inhibits the
CC expression of vimentin positive astrocytes with high anti-inflammatory
CC effect. Hirudin or its derivs. are used to prepare conventional
CC pharmaceutical prepns. for admin. by drip infusion or local injection
CC at a dosage of about 0.001-5 mg/day for a male adult patient.
XX
SQ Sequence 65 AA;

Query Match 100.0%; Score 368; DB 18; Length 65;
Best Local Similarity 100.0%; Pred. No. 1.8e-28;
Matches 65; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Qy       1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60
           ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60

Qy      61 EEYLQ 65
           |||||
Db      61 EEYLQ 65
```

RESULT 7
AAB70828
ID AAB70828 standard; Protein; 65 AA.
XX
AC AAB70828;
XX
DT 18-JUN-2001 (first entry)
XX
DE S. marcescens hirudin protein fragment.
XX
KW Hirudin; outer membrane protein; oprF; lambB; fumarate reductase;
KW Leu-hirudin; Leu1-Thr2-63-desulfato-hirudin; antithrombotic.
XX
OS Serratia marcescens.
XX
PN DE19944870-A1.
XX
PD 29-MAR-2001.
XX
PF 18-SEP-1999; 99DE-1044870.
XX
PR 18-SEP-1999; 99DE-1044870.
XX
PA (AVET) AVENTIS PHARMA DEUT GMBH.
XX
PI Habermann P, Bender R;
XX
DR WPI; 2001-246103/26.
DR N-PSDB; AAF61507.
XX
PT Hirudin precursor containing heterologous signal peptide, useful for
PT recombinant production of antithrombotic Leu-hirudin, is efficiently
PT secreted and processed -
XX
PS Disclosure; Page 9; 12pp; German.
XX
CC This invention describes a novel hirudin precursor (I), comprising the
CC signal sequence from the outer membrane protein of Serratia marcescens,
CC the oprF protein of Pseudomonas fluorescens, the lambB protein of
CC Escherichia coli, or the fumarate reductase of Shewanella putrefaciens,
CC with the Leu-hirudin (LH) ((Leu1-Thr2)-63-desulfato-hirudin) sequence
CC linked to the C-terminus of the signal sequence. (I) is an intermediate
CC in recombinant production of LH, a known antithrombotic. The specified
CC signal sequence may also be used for secretory expression of other
CC proteins. (I) is processed directly to LH and this, in native form,
CC secreted from E. coli in high yield. This results, both during
CC fermentation and subsequent purification, in a higher concentration of
CC hirudin, reducing costs of production. The specified signal sequences
CC provide more efficient secretion than known sequences. This sequence
CC represents a fragment of the S. marcescens hirudin protein.
XX
SQ Sequence 65 AA;

Query Match 100.0%; Score 368; DB 22; Length 65;
Best Local Similarity 100.0%; Pred. No. 1.8e-28;
Matches 65; Conservative 0; Mismatches 0; Indels 0; Gaps 0;

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Db       1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60

Qy      61 EEYLQ 65
           |||||
Db      61 EEYLQ 65
```

RESULT 8
ABB08618
ID ABB08618 standard; protein; 127 AA.
XX
AC ABB08618;
XX
DT 10-APR-2002 (first entry)
XX
DE Hir(1-65)/AspPro/TAP(1-60) fusion protein.
XX
KW Fusion protein; hirudin; Hir; tick anticoagulant protein; TAP;
KW anticoagulant; blood; thrombin; factor Xa.
XX
OS Chimeric - Hirudo medicinalis.
OS Chimeric - Ornithodoros moubata.
OS Synthetic.
XX
FH Key Location/Qualifiers
FT Region 1..65
FT /label= hirudin
FT Region 66..67
FT /label= Asp/Pro_linker
FT Region 68..127
FT /label= TAP
XX
PN WO200204486-A2.
XX
PD 17-JAN-2002.
XX
PF 27-JUN-2001; 2001WO-EP07333.
XX
PR 07-JUL-2000; 2000DE-1033195.
XX
PA (AVET) AVENTIS PHARMA DEUT GMBH.
XX
PI Habermann P;
XX
DR WPI; 2002-154918/20.
XX
PT New fusion protein of hirudin and tick anticoagulant protein, useful as
PT an anticoagulant -
XX
PS Example 4; Page -; 36pp; German.
XX
CC The invention relates to a bifunctional fusion protein comprising

```
CC   hirudin or its variant and tick anticoagulant protein (TAP) or its
CC   variant. The fusion proteins have anticoagulant activity and are used to
CC   inhibit coagulation of blood by acting to inhibit thrombin and inhibit
CC   factor Xa. The present sequence is that of the Hir(1-65)/AspPro/TAP(1-60)
CC   fusion protein useful in the illustration of the invention.
CC   Note: The present sequence is not given in the specification but is
CC   derived from SEQ ID NO 15 (ABB08605) and SEQ ID NO 17 (ABB08606).
XX
SQ   Sequence   127 AA;

  Query Match             100.0%;  Score 368;  DB 23;  Length 127;
  Best Local Similarity   100.0%;  Pred. No. 3.4e-28;
  Matches   65;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy      1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60

Qy     61 EEYLQ 65
          |||||
Db     61 EEYLQ 65


RESULT 9
AAW13896
ID   AAW13896 standard; Protein; 65 AA.
XX
AC   AAW13896;
XX
DT   14-MAY-1997  (first entry)
XX
DE   Hirudin variant (des-Val 1, Thr 2)-desulphato hirudin HV1.
XX
KW   Hirudin; variant; thrombin inhibitor; human; acetylsalicylic acid; ASA;
KW   thrombolytic agent; cardiovascular event; stroke; cardiovascular death;
KW   coronary re-vascularisation; therapy; acute myocardial infarction; AMI;
KW   hirudo medicinalis.
XX
OS   Synthetic.
XX
FH   Key             Location/Qualifiers
FT   Misc-difference 1
FT                   /note= "D-form residue"
FT   Misc-difference 2
FT                   /label= V2T
FT   Modified-site   63
FT                   /note= "modified with phenolic hydroxy group"
XX
PN   EP732102-A2.
XX
PD   18-SEP-1996.
XX
PF   12-MAR-1996;   96EP-0103821.
XX
PR   12-MAY-1995;   95US-0440556.
PR   15-MAR-1995;   95US-0405269.
XX
PA   (BEHW ) BEHRINGWERKE AG.
PA   (BGHM ) BRIGHAM & WOMENS HOSPITAL.
XX
PI   Heinrichs H,  Hennekens CH;
XX
DR   WPI; 1996-414245/42.
XX
PT   Composition comprising acetyl:salicylic acid and hirudin - is esp.
PT   useful for preventing the recurrence of acute myocardial
PT   infarction(s)
XX
PS   Claim 6; ; 11pp; English.
XX
CC   AAW13889-W13898 represent mutations of the hirudin variants represented
CC   by AAR99354-R99356.  Hirudin is a direct thrombin inhibitor, which has a
CC   very high affinity for human (as well as other mammalian species)
CC   thrombin. One molecule binds to a thrombin molecule, forming a tight
CC   noncovalent complex and thereby irreversibly inactivates thrombin.  These
CC   sequences can be used in a composition of the invention, which also
CC   contains acetylsalicylic acid (ASA).  The composition may be administered
CC   to patients not undergoing treatment with a thrombolytic agent, to
CC   inhibit and/or prevent myocardial or cardiovascular events (including
CC   myocardial infarctions, strokes, coronary re-vascularisation or
CC   cardiovascular death) in the patient. The compositions of the invention
CC   are especially useful for preventing the recurrence of acute myocardial
CC   infarctions (AMI).  The components ASA and hirudin act synergistically.
CC   The combined use of ASA and hirudin in AMI patients where thrombolytic
CC   treatment is not advisable is expected to result in a higher incidence of
CC   open coronary vessels.
XX
SQ   Sequence   65 AA;

  Query Match             99.2%;  Score 365;  DB 17;  Length 65;
  Best Local Similarity   98.5%;  Pred. No. 3.4e-28;
  Matches   64;  Conservative    1;  Mismatches    0;  Indels    0;  Gaps    0;

Qy      1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60
          :|||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1 VTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60

Qy     61 EEYLQ 65
          |||||
Db     61 EEYLQ 65


RESULT 10
AAP50082
ID   AAP50082 standard; protein; 64 AA.
XX
AC   AAP50082;
XX
DT   22-OCT-1991  (first entry)
XX
DE   Anticoagulant peptide.
XX
KW   Anticoagulant; diagnosis;
XX
OS   Hirudo medicanalis.
XX
PN   EP158986-A.
XX
PD   23-OCT-1985.
XX
PF   12-APR-1985;   85EP-0104445.
XX
PR   18-APR-1984;   84DE-3414593.
PR   19-OCT-1984;   84DE-3438296.
XX
PA   (FARH ) HOECHST AG.
XX
PI   Tripier D;
XX
DR   WPI; 1985-264974/43.
XX
PT   New polypeptide cpds. with anticoagulant activity - extracted from
PT   leeches and synthetic analogues.
XX
PS   Disclosure; page 2; 24pp; german.
XX
CC   The peptide and its cleavage prods. are useful as anticoagulants. They
CC   are specific stoichiometric inhibitors of thrombin, so can be used
CC   therapeutically or as reagents for diagnosis. The C-terminal Tyr residue
CC   has a phenolic H or phenol ester gp., pref. H, SO3H or PO3H2.
XX
SQ   Sequence   64 AA;

  Query Match             98.9%;  Score 364;  DB 6;  Length 64;
  Best Local Similarity   100.0%;  Pred. No. 4.2e-28;
  Matches   64;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;
```

```
Qy      2 TYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIPE 61
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1 TYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIPE 60

Qy     62 EYLQ 65
          ||||
Db     61 EYLQ 64
```

RESULT 11
AAR59773
ID AAR59773 standard; peptide; 64 AA.
XX
AC AAR59773;
XX
DT 17-FEB-1995 (first entry)
XX
DE Desulphatohirudin.
XX
KW Desulphatohirudin; varient; sulphate monoester group; hirudin;
KW depot formulation; deep vein thrombosis; water; calcium; magnesium;
KW zinc; ions; water-insoluble salt; stability; bleeding.
XX
OS Hirudo medicinalis.
XX
PN NZ250895-A.
XX
PD 27-JUN-1994.
XX
PF 16-FEB-1994; 94NZ-0250895.
XX
PR 18-FEB-1993; 93GB-0003275.
XX
PA (CIBA) CIBA GEIGY AG.
XX
PI Arvinte T;
XX
DR WPI; 1994-214991/26.
XX
PT Aq depot formulations for treatment of e.g. deep vein thrombosis
PT - comprises water, hirudin, and a water-soluble salt of calcium,
PT magnesium or zinc
XX
PS Disclosure; Page 3-4; 24pp; English.
XX
CC This sequences is a desulphatohirudin varient which lacks the sulphate
CC monoester group at Tyr63 of natural hirudin. These proteins have
CC approximately the same biological activity as natural, sulphated
CC hirudin. These proteins can be used in the depot formulation of the
CC invention for the treatment of deep vein thrombosis. The formulations
CC comprise water, a hirudin or a hirudin variant and calcium, magnesium
CC or zinc ions in the form of water-insoluble salts. These formulations
CC have improved stability. When the hirudin is administered using this
CC formulation it has been found that there is less bleeding around the
CC injection site than when it is administered as a simple solution.
XX
SQ Sequence 64 AA;

```
  Query Match           98.6%;  Score 363;  DB 15;  Length 64;
  Best Local Similarity  100.0%;  Pred. No. 5.3e-28;
  Matches   64;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy      1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60
          ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60

Qy     61 EEYL 64
          ||||
Db     61 EEYL 64
```

RESULT 12
AAP50329
ID AAP50329 standard; protein; 65 AA.
XX
AC AAP50329;
XX
DT 12-NOV-1991 (first entry)
XX
DE Hirudin protein.
XX
KW Hirudin; anticoagulant; thrombosis; diagnosis;
XX
OS Hirudo medicinalis.
XX
PN WO8504418-A.
XX
PD 10-OCT-1985.
XX
PF 27-MAR-1985; 85WO-FR00062.
XX
PR 27-MAR-1984; 84FR-0004755.
PR 27-APR-1984; 84FR-0013250.
XX
PA (TRAN-) TRANSGENE SA.
XX
PI Tolstoshev P, Harvey R, Courtney M, Lecocq J-P;
XX
DR WPI; 1985-263187/42.
XX
PT Cloning and expression vector contg. DNA for hirudin - or analogues,
PT useful as anticoagulant.
XX
PS Disclosure; Fig. 1; 92pp; French.
XX
CC DNA encoding hirudin or its analogues can be inserted into cloning
CC and expression vectors comprising an origin of replication for
CC pBR322, a promoter (esp. all/part of a lambda phage), and an
CC initiation region, specifically the sequence ATAACACAGGAACATCTATG.
CC It may also contain all/part of gene N from lambda and/or a gene
CC encoding antibiotic resistance. The vector is esp. pTG 720, 718 and
CC 719. Hirudin is a known anticoagulant for treating venous
CC thrombosis, vascular occlusions or intravenous disseminated
CC coagulation. When applied topically it may be used to treat
CC haemorrhoids, varicose veins, oedema or psoriasis. Hirudin can also
CC be used in extracorporeal blood circulation systems, as a
CC diagnostic reagent to detect the formn. of clots (when labelled),
CC and as an additive to laboratory blood samples. Using the vector
CC hirudin can now be produced in large quantities and of consistent
CC quality.
XX
SQ Sequence 65 AA;

```
  Query Match           97.8%;  Score 360;  DB 6;  Length 65;
  Best Local Similarity  96.9%;  Pred. No. 1e-27;
  Matches   63;  Conservative    1;  Mismatches    1;  Indels    0;  Gaps    0;

Qy      1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60
          : ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db      1 VVYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60

Qy     61 EEYLQ 65
          |||||
Db     61 EEYLQ 65
```

RESULT 13
AAP50335
ID AAP50335 standard; protein; 65 AA.
XX
AC AAP50335;
XX
DT 12-NOV-1991 (first entry)
XX
DE Hirudin variant.

```
XX
KW   Hirudin; variant; anticoagulant; thrombosis; diagnosis;
XX
OS   Hirudo medicinalis.
XX
PN   WO8504418-A.
XX
PD   10-OCT-1985.
XX
PF   27-MAR-1985;   85WO-FR00062.
XX
PR   27-MAR-1984;   84FR-0004755.
PR   27-APR-1984;   84FR-0013250.
XX
PA   (TRAN-) TRANSGENE SA.
XX
PI   Tolstoshev P,  Harvey R,  Courtney M,  Lecocq J-P;
XX
DR   WPI; 1985-263187/42.
XX
PT   Cloning and expression vector contg. DNA for hirudin - or analogues,
PT   useful as anticoagulant.
XX
PS   Claim 27; page 62; 92pp; French.
XX
CC   The hirudin variant has the following amino acid substns.: 24 Lys to
CC   Gln, 33 Asn to Asp, 35 Lys to Glu, 36 Gly to Lys, 47 Asn to Lys, 49
CC   Glu to Gln, and 53 Asn to Asp. DNA encoding hirudin or its analogues
CC   can be inserted into cloning and expression vectors comprising an origin
CC   of replication for pBR322, a promoter (esp. all/part of a lambda phage),
CC   and an initiation region, specifically the sequence ATAACACAGGAACATCTATG.
CC   It may also contain all/part of gene N from lambda and/or a gene
CC   encoding antibiotic resistance. The vector is esp. pTG 720, 718 and
CC   719. Hirudin is a known anticoagulant for treating venous
CC   thrombosis, vascular occlusions or intravenous disseminated
CC   coagulation. When applied topically it may be used to treat
CC   haemorrhoids, varicose veins, oedema or psoriasis. Hirudin can also
CC   be used in extracorporeal blood circulation systems, as a
CC   diagnostic reagent to detect the formn. of clots (when labelled),
CC   and as an additive to laboratory blood samples. Using the vector
CC   hirudin can now be produced in large quantities and of consistent
CC   quality.
XX
SQ   Sequence   65 AA;

  Query Match             97.8%;  Score 360;  DB 6;  Length 65;
  Best Local Similarity   96.9%;  Pred. No. 1e-27;
  Matches   63;  Conservative    1;  Mismatches    1;  Indels    0;  Gaps    0;

Qy       1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60
           : |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1 VVYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60

Qy      61 EEYLQ 65
           |||||
Db      61 EEYLQ 65


RESULT 14
AAP50188
ID   AAP50188 standard; peptide; 65 AA.
XX
AC   AAP50188;
XX
DT   25-NOV-1991  (first entry)
XX
DE   Desulphatohirudine derivative.
XX
KW   Desulphatohirudine; derivative; blood coagulation; thrombin assay;
KW   anticoagulant.
XX
OS   Helix pomatia.
XX
PN   EP142860-A.
XX
PD   29-MAY-1985.
XX
PF   20-NOV-1984;   84EP-0114038.
XX
PR   22-NOV-1983;   83DE-3342139.
XX
PA   (CIBA ) CIBA GEIGY AG.
PA   (PLAN-) PLANTORGAN WERK.
XX
PI   Seemuller U,  Dodt J,  Fritz H,  Fink E;
XX
DR   WPI; 1985-129636/22.
XX
PT   New desulphatohirudin drivs. with anticoagulant activity - prepd.
PT   from hirudin by hydrolytic desulphation.
XX
PS   Claim 1; page 1; 23pp; german.
XX
CC   The desulphatohirudine derivative is made from hirudin by hydrolytic
CC   desulphation. The Cys residues are joined together in pairs by
CC   disulphide bridges. The derivative is useful for inhibiting blood
CC   coagulation in human or veterinary medicine, and can also be used as
CC   a reagent for the clinical assay of thrombin. It is formulated for
CC   injection (0.01-0.05 mg/kg) or topical application. The derivative
CC   is better suited to biotechnical prodn. than hirudin, which contains
CC   a sulphate ester residue.
XX
SQ   Sequence   65 AA;

  Query Match             97.8%;  Score 360;  DB 6;  Length 65;
  Best Local Similarity   96.9%;  Pred. No. 1e-27;
  Matches   63;  Conservative    1;  Mismatches    1;  Indels    0;  Gaps    0;

Qy       1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60
           : |||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1 VVYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60

Qy      61 EEYLQ 65
           |||||
Db      61 EEYLQ 65


RESULT 15
AAP70225
ID   AAP70225 standard; protein; 65 AA.
XX
AC   AAP70225;
XX
DT   03-OCT-2002  (updated)
DT   02-APR-1991  (first entry)
XX
DE   Sequence of desulphatohirudin variant 1 (HIV).
XX
KW   Anticoagulant; thrombin inhibitor.
XX
OS   Unidentified.
XX
PN   EP225633-A.
XX
PD   16-JUN-1987.
XX
PF   09-DEC-1986;   86EP-0117098.
XX
PR   29-MAY-1986;   86GB-0013088.
PR   12-DEC-1985;   85GB-0030631.
XX
PA   (CIBA ) CIBA GEIGY AG.
PA   (PLAN-) PLANTORGAN WERK HEINRRICH.
PA   (CHRI-) PLANTORGANW CHRISTENSEN.
XX
PI   Meyhack B,  Marki W,  Heim J;
```

XX
DR WPI; 1987-164868/24.
DR N-PSDB; AAN70319.
XX
PT New DNA constructs and hybrid vectors for transformation of yeast
PT etc. - useful for prodn. and secretion of protein with hirudin
PT activity for use as thrombin inhibitors.
XX
PS Claim 11; p128; 146pp; English.
XX
CC The preferred DNA construct of the invention contains the PHO5
CC promoter and a DNA segment consisting of the PHO5 signal sequence
CC upstream of and in reading frame with a DNA sequence coding for
CC mature desulphatohirudin. The segment is under the transcriptional
CC control of the PHO5 promoter and the 3' flanking sequence of the
CC PHO5 gene.
CC (Updated on 03-OCT-2002 to add missing OS field.)
XX
SQ Sequence 65 AA;

Query Match 97.8%; Score 360; DB 8; Length 65;
Best Local Similarity 96.9%; Pred. No. 1e-27;
Matches 63; Conservative 1; Mismatches 1; Indels 0; Gaps 0;

```
Qy       1 LTYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60
           : ||||||||||||||||||||||||||||||||||||||||||||||||||||||||||||
Db       1 VVYTDCTESGQNLCLCEGSNVCGQGNKCILGSDGEKNQCVTGEGTPKPQSHNDGDFEEIP 60

Qy      61 EEYLQ 65
           |||||
Db      61 EEYLQ 65
```

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